REMARKS

The Title has been amended as requested by the Examiner. Claims 8, 10, 11 and 39 have been amended to more clearly define Applicants' invention. Support for the amendments can be found, for example, on page 6, lines 23-24, of the specification. New claims 49-55 have been added. Support for the new claims can be found, for example, on page 5, lines 1-4 of the specification, page 8, lines 8-11, page 10, lines 10-12 and in the original claims. No new matter has been added. Claims 3, 4, 6, 8-12, 14 and 30-55 are pending. Claims 3, 8, 39, 49-52 and 54 are independent.

Objections

Title

The Examiner has objected to the Title. See page 2 of Office Action. Applicants have replaced the original Title with a new Title as requested by the Examiner. Applicants respectfully request reconsideration and withdrawal of this objection.

Claim 10

The Examiner objects to claim 10 because "the claim appears to contemplate the use of additives that clearly conflict with the limitation of 'dry finely divided particles'. " See page 3 of Office Action. Claim 10 depends from independent claim 8. Claim 8 includes the transitional phrase "comprising" which is open ended. Claim 8 relates to a formulation that "comprising" a pharmaceutically acceptable powder. The additive of claim 10 is present in addition to the dry, finely divided particles. Applicants therefore respectfully request withdrawal of this objection.

Claim 11

The Examiner has objected to claim 11 because the claim "recites a concentration in units (mg/ml) indicating a fluid composition, conflicting with the 'dry' limitation in claim 8." See page 3 of Office Action. Applicants respectfully disagree. The unit of mg/mL merely reflects a mass per unit volume measurement; the unit does not relate to the physical state of the material. Indeed, a "dry" material has a volume that can be expressed in ml. In the interest of advancing

prosecution, claim 11 has been amended to clarify that the concentration relates to that of the glucocorticosteroid in the formulation. Applicants respectfully request withdrawal of this objection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 3, 4, 8-12, 30-34, 36-44, and 46 are rejected under 35 U.S.C. § 112 as being indefinite. See page 3 of the Office Action. Claims 3, 8 and 39 are independent claims. The Examiner raises three grounds of rejection.

First, the Examiner contends that the term "glucocorticosteroid" is indefinite. See page 3 of Office Action. Applicants respectfully disagree. A person of ordinary skill in the art would understand the meaning of the term glucocorticosteroid. See, for example, the references attached at Tab A, Tab B and Tab C. One suitable definition for the term "glucocorticosteroid," according to the reference at Tab A is "any naturally occurring or synthetic hormonal corticosteroid that acts primarily on carbohydrate and protein metabolism." Applicants respectfully request reconsideration and withdrawal of this rejection.

Second, the Examiner contends that the claims are indefinite because they recite:

> a glucocorticosteroid or ester, or acetal, or salt thereof wherein the glucorticosteroid ...comprises an asymmetric acetal structure.' It is not clear if the compound of the invention requires an asymmetric structure, or when the glucocorticosteroid does have an acetal structure, it must be asymmetric one. (See page 4 of Office Action).

Glucocorticosteroids with an asymmetric structure are discussed in the specification. See, for example, page 4, lines 17-30 to page 5, lines 1-4 of the specification. One of ordinary skill in the art would understand that the claims include glucocorticosteroids including an asymmetric acetal structure, regardless of whether it is a glucocorticosteroid, an acetal of a glucocorticosteroid, an ester of a glucocorticosteroid, or a salt of glucocorticosteroid. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Third, the Examiner contends "[r]egarding claim 10, the limitation 'the suspension' lacks adequate antecedent basis." See page 4 of Office Action. Applicants have amended claim 10 to

more clearly describe Applicants' invention. Applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants' Invention

Applicants have discovered a pharmaceutically acceptable powder, and a sterile pharmaceutical formulation including the powder. See independent claims 3, 8 and 39. The **pharmaceutically acceptable powder is in the form of dry, finely divided particles**. **The dry particles are sterilized** and include a glucocorticosteroid or ester, acetal, or salt thereof. See independent claims 3, 8 and 39.

Rejection under 35 U.S.C. § 102(b)

Claims 10 and 11 have been rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 3,962,430 to O'Neill *et al.* ("O'Neill"). Claim 10 and 11 depend from independent claim 8.

In making the rejection, the Examiner contends "[t]his reference does not disclose a sterile, dry solid, as recited in the claim from which these claims depend. However, when a sterile solution/suspension of the glucocorticosteroid is prepared and sterilized, it is indistinguishable from one prepared from a sterile, dry solid." See page 4 to 5 of the Office Action.

O'Neill does not disclose a **powder in the form of dry, finely divided particles, the dry particles being sterilized**. See independent claim 8. Rather, O'Neill describes sterilizing a drug suspended in an aqueous mixture by autoclaving (sterilization with steam under high temperature and pressure) or tyndalization. See the abstract and column 2, lines 11-36. In other words, O'Neill sterilizes the suspended drug in an aqueous mixture.

The Examiner acknowledges that O'Neill does not describe a sterile, dry solid. See page 5 of the Office Action. But also, O'Neill does not describe a sterile formulation including **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. The sterile solution/suspension of the glucocorticosteroid as taught by O'Neill is not a formulation including powder in the form of dry, finely divided particles, the dry particles being sterilized.

For at least these reasons, claims 10 and 11 which depend from independent claim 8 are not anticipated by O'Neill. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. § 102(e)

Claims 10 and 11 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,241,69 to Saidi *et al.* ("Saidi"). Claim 10 and 11 depend from independent claim 8.

In making the rejection, the Examiner contends that "when a sterile solution/suspension of the glucocorticosteroid is prepared and sterilized, it is indistinguishable from one prepared from a sterile, dry solid." See page 4 to 5 of the Office Action.

Saidi does not disclose a sterile formulation including a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. See independent claim 8. As acknowledged by the Examiner, Saidi does not disclose a "sterile, dry solid." See page 5 of the Office Action. Indeed, Saidi does not describe a sterile formulation including dry, finely divided particles, the dry particles being sterilized. Instead, Saidi describes aqueous solutions which are sterilized by passing the solution through a sterile filter. See Examples 1-4 of Saidi.

For at least these reasons, claims 10 and 11 which depend from independent claim 8 are not anticipated by Saidi. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

Jakupovic combined with Bussey

Claims 3, 4, 6, 8-10, 12, 14, 34-36, 39, 41, 42 and 45-48 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/32095 to Jakupovic *et al.* ("Jakupovic") combined with Bussey *et al.* ("Bussey"). See page 6 to 8 of the Office Action.

Claims 4, 6, 9-12, 14, 30-31, 34-36, 41, 42 and 45-48 depend from independent claims 3, 8 and 39.

The Examiner contends that:

> [i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the respirable, dry powders disclosed by JAKUPOVIC by either irradiation or treatment with ethylene oxide. The artisan would have been motivated to sterilize the respirable particles to prevent microbial growth in the packaged material. The artisan would be particularly motivated to sterilize the glucocorticosteroid in the form which it is intended to be used (see page 7 of the Office Action).

Jakopovic does not teach or suggest a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. See independent claims 3, 8 and 39. As acknowledged by the Examiner on page 7 of the Office Action, Jakopovic does not teach or suggest a dry sterile powder. Indeed, Jakopovic merely teaches an inhalation compound which is dissolved in a solvent. See Jakopovic at page 5, lines 29-30 to page 6, lines 1-3. In Jakopovic, the "choice of solvent depends upon the solubility of the compound to be dissolved. Preferably, a substantially saturated or supersaturated solution is obtained." See Jakopovic at page 5, line 30 to page 6, line 1. Nothing in Jakopovic suggests or provides motivation to produce a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**.

Bussey does not teach or suggest **a pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. Bussey merely teaches bulk sterilization of corticosteroids by ^{60}Co irradiation. Indeed, Table III of Bussey only teaches the following corticosteroids, namely Hydrocortisone acetate, Isoflupredone acetate, Methylprednisolone acetate and Predinisolone Hydrous as corticosteroids. See page 54 of Bussey. Bussey also shows amounts of degradation upon ^{60}Co irradiation. See Table III, page 54 of Bussey. Bussey is not concerned with producing a pharmaceutically acceptable powder. Bussey does not suggest or provide motivation to produce a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**.

Moreover, there is no motivation to combine Jakopovic and Bussey to arrive at a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. Indeed, neither Jakopovic or Bussey, nor their combination provide the motivation to provide **pharmaceutically acceptable powder in the form of dry, finely**

divided particles, the particles being sterilized. Applicants submit that the Examiner is using hindsight to combine Jakopovic combined with Bussey. The motivation the Examiner refers to is not related to the teachings of the references. Obviousness cannot be established simply by stitching together pieces of prior art using the patent as a template. See Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985); see also Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 873 (Fed. Cir. 1985) (denouncing courts' tendency to depart from proper standard of nonobviousness "to the tempting but forbidden zone of hindsight."); In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). The cited references must provide some suggestion, motivation, or teaching for combining known components. See Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed.Cir.1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination."); C.R. Bard, Inc. v. M3 Systems, Inc., 157 F.3d 1340 (Fed. Cir. 2000). The requisite motivation to combine the references has not been provided.

For at least these reasons, independent claims 3, 8 and 39 and dependents 4, 6, 9-12, 14, 30-31, 34-36, 41, 42 and 45-48 therefrom are patentable over Jakopovic combined with Bussey. Applicants respectfully request reconsideration and withdrawal of this rejection.

Jakupovic combined with Bussey further combined with Radhakrishnan and Sequiera

In the Office Action, the Examiner has rejected:

(I) Claims 3, 4, 6, 8-10, 12, 14, 34-36, 39, 41, 42 and 45-48 under 35 U.S.C. § 103(a) as being unpatentable over Jakupovic combined with Bussey and U. S. Patent No. 5,192,528 to Radhakrishan ("Radhakrishnan") (see pages 8 to 9 of the Office Action) and

(II) Claims 3, 4, 6, 8-12, 14, 30, 31, 34-36, 38, 39 and 41-48 under 35 U.S.C. § 103(a) as being unpatentable over Jakopovic combined with Bussey and U.S. Patent to Sequiera ("Sequiera") (see page 9-10 of the Office Action).

Claims 4, 6, 9-12, 14, 30, 31, 34-36, 38, 39, 41-48 depend from independent claims 3, 8 and 39.

As discussed above, neither Jakopovic nor Bussey teach or suggest a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. None of Radhakrishnan or Sequeira overcomes the deficiencies of Jakopovic and Bussey since Radhakrishnan or Sequeira do not teach or suggest a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**.

Radhakrishnan discloses an aqueous liposome suspension. See abstract of Radhakrishnan. Radhakrishnan is not concerned with a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. Sequiera teaches "treating of corticosteroid-responsive diseases of the upper and lower airway passages and lungs, such as asthma, by orally or intranasally administering to said passages and lungs an amount of mometasone furoate." See col. 1, lines 19-23 of Sequeira. Sequiera is not concerned with **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**.

For at least these reasons, independent claims 3, 8 and 39 and dependent claims 4, 6, 9-12, 14, 30-31, 34-36, 41, 42 and 45-48 therefrom are patentable over Jakopovic combined with Bussey, Radhakrishnan and Sequiera. Applicants respectfully request reconsideration and withdrawal of this rejection.

Radhakrishnan

Claims 10 and 11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Radhakrishnan. See pages 10-11 of the Office Action. Claims 10 and 11 depend from independent claim 8.

In making the rejection, the Examiner contends that

> [i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the liposomal solution by filtration. The artisan would have been motivated to sterilize the solution to prevent microbial growth in the pharmaceutical preparation (see page 10 to page 11 of the Office Action).

As discussed above, independent claim 8 relates to a sterile formulation including a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. As acknowledged by the Examiner, Radhakrishnan "teaches that the liposomal preparations can be sterilized by filtration, but a sterilized composition is not specifically exemplified." See page 10 of Office Action. But, as discussed above, Radhakrishnan is not concerned with a sterile formulation including a **pharmaceutically acceptable powder in the form of dry, finely divided particles, the dry particles being sterilized**. There is no motivation in the teaching of Radhakrishnan to do so. Radhakrishnan does not teach or suggest a sterile pharmaceutical formulation which includes **a pharmaceutically acceptable powder is in the form of dry, finely divided particles, the dry particles being sterilized.** For at least there reasons, independent claim 8, and dependent claims 10 and 11, are patentable over Radhakrishnan. Applicants respectfully request reconsideration and withdrawal of this rejection.

New Independent Claims

None of the cited references describe, teach or suggest a **pharmaceutically acceptable powder in the form of heat sterilized, dry, finely divided particles including budesonide, rofleponide and rofleponide palmitate** or ester, acetal, or salt thereof. See independent claims 49-51. None of the cited references describe, teach or suggest a **powder in the form of heat sterilized, dry, finely divided particles including a glucocorticosteroid** or ester, acetal or salt thereof. See independent claim 52. None of the cited references describe, teach or suggest a **pharmaceutically acceptable suspension including a sterilized, finely divided particles of budesonide, rofleponide and rofleponide palmitate or ester, acetal, or salt thereof combined with a pharmiceutically acceptable additive**. See independent claim 54. Thus, claims 49-55 are allowable.

Attached is a marked-up version of the changes being made by the current amendment.

CONCLUSION

Applicant asks that all claims be allowed. Enclosed is a check in payment for additional claim fees. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Jun 12, 02

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Version with markings to show changes made

In the Title:

Title beginning at page 1, line 1 has been amended as follows:

Replace the original title "New Composition of Matter" with -- Sterile Pharmaceutically Acceptable Formulations and Methods for Producing the Same --.

In the claims:

New claims 49-55 have been added.

Claims 3, 8, 10-11 and 39 have been amended as follows:

--3. (Amended) A pharmaceutically acceptable powder in the form of dry, finely divided particles having a mass median diameter (MMD) of less than 10 μm, said **[powder] dry particles** being sterilized and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, comprises an asymmetric acetal structure.--

--8. (Amended) A sterile pharmaceutical formulation comprising a pharmaceutically acceptable powder in the form of dry, finely divided particles, said **[powder] dry particles** being sterilized and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, comprises an asymmetric acetal structure, and wherein at least 80% of the particles have a mass median diameter (MMD) of less than 10 μm.--

--10. (Amended) The sterile pharmaceutical formulation according to claim 8, comprising at least one additive selected from the group consisting of surfactants, pH regulating agents, chelating agents, agents rendering the **formulation [suspension]** isotonic and thickening agents.--

--11. (Amended) The sterile pharmaceutical formulation according to claim 8, wherein the concentration of the glucocorticosteroid or ester, acetal, or salt thereof, ranges from about 0.05 to about 20 mg/ml **in the formulation**.--

--39. (Amended) A pharmaceutically acceptable powder in the form of dry, finely divided particles having a mass median diameter (MMD) of less than 10 μm, said **[powder] dry particles** being sterilized by heat treatment at a temperature of from 100°C to 130°C and comprising a glucocorticosteroid or ester, acetal, or salt thereof, wherein the glucocorticosteroid or ester, acetal, or salt thereof, comprises an asymmetric acetal structure.--